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TARGET ORGAN REMODELING FEATURES IN PATIENTS WITH ESSENTIAL HYPERTENSION IN COMBINATION WITH DIABETES AND OBESITY

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Abst ract
This article demonstrates the results of the comparative analysis of parameters of the structural and functional heart, blood vessels and liver remodeling in patients with essential hypertension combined with diabetes mellitus type 2 and obesity. It was established that irrespective of BMI the patients with essential hypertension and diabetes mellitus type 2 in comparison with hypertensive patients had different values of thickness of the intima-media in the carotid arteries (which were significantly higher), different pulse wave velocity in the great vessels, the size of the cavities and myocardial mass of the left ventricle, the integral index of diastolic filling E/e (integral ratio of maximum velocities of early diastolic filling according to spectral and tissue Doppler studies), the index of rigidity of the liver parenchyma according to shift-wave elastography and significantly lower value of endothelium-dependent vasodilatation of the brachial artery ($p<0.05$). Even a slight increase in body mass index (not higher than 34.9 kg/m$_2$) was associated with a deterioration of endothelial function and structural and functional properties of heart, blood vessels, liver, which is more pronounced in terms of comorbidity.

Keywords: *essential hypertension, type 2 diabetes, obesity, remodeling of heart, vessels and liver.*

Introduction

In the general structure of causes of death inUkraine, the proportion of cardiovascular mortality in 2014 was 66.5%. About 90% of deaths are associated with severe forms of ischemic heart disease and stroke, the majority of which progresses on the background of arterial hypertension. Arterial hypertension is one of the most common cardiovascular diseases in most European countries, with about 90% of its essential form being essential hypertension [*Kovalenko VM, Karnatskyi VM, 2014*]. The incidence of coronary
heart disease and stroke in people with arterial hypertension increases 3-4 and 7 times, respectively [*Gorbas IM et al., 2010; Pospelov DL, 2013; Kovalenko VM, Karnatskyi VM, 2014*].

Along with arterial hypertension, the top threeof the most common diseases in the world are represente by diabetes mellitus type 2 (DM2) and obesity [*American Diabetes Association, 2011; Kovalenko VM, Karnatskyi VM, 2014*]. The WHO forecasts an increase in number of patients with DM2 to 380 million before 2025 [*Bagry HS et al., 2008*] and signs of overweight among 50% of the population of our planet [*Cole T et al., 2000; Ametov AS, 2002; Dedov II, Melnichenko GA, 2004*].

Concomitants to arterial hypertension, DM2 and obesity are associated with increased risk of cardiovascular events [*Rabmouni K et al., 2005; Bagry HS et al., 2008; Shilov AM et al., 2009; Demidova TY, 2011; Syrenko YM, 2010; Colwell JA, 2011; Butrova SA, 2012*]. Increased risk of cardiovascular events in patients with comorbid disorders, provided by a combination of arterial hypertension with DM2 or arterial hypertension with obesity, due to a common mechanism for the progression of these diseases – activation of sympathoadrenal and renin-angiotensin-aldosteronesystems, oxidative stress, systemic inflammation, as well as hyperinsulinemia, hyperleptinemia, hypoadiponektinemia, and dyslipidemia [*Thomas F et al., 2005; Narkiewicz K, 2006; Guize L et al., 2007*]. The implementation of these mechanisms in comorbidity leads to a continuously progressive remodeling of the vital organs [*Kochueva MN et al., 2014*].

Cardiac remodeling is manifested by impaired normal geometry, slow relaxation and increased stiffness of the myocardium, decreased myocardial contractility, which eventually leads to the progression of heart failure [*Abel ED et al., 2008; Khurs EM, Poddubnaya AV, 2010*]. Impairment of structural and functional state of the vascular wall is manifested by decreasing endothelium-dependent vasodilatation of the brachial artery, increasing intima-media thickness in the carotid arteries and pulse wave velocity in the great vessels: the carotid artery and the abdominal aorta [*Intengan HD, Schiffrin EL, 2001*; *Kochueva MN et al., 2014*; *Shalimova AS, 2014*]. The patients with arterial hypertension in combination with DM2 and obesity are characterized by metabolic liver damageinitiated by hyperinsulinemia and insulin resistance, which lead to the increasing activity of enzymes that split triglycerides, fatty tissue, increase blood concentrations of free fatty acids and their accumulation in the cytoplasm of hepatocytes, and development of non-alcoholic fatty liver disease. It begins with steatosis and can transform into steatohepatitis and cirrhosis. The first manifestationsof non-alcoholic fatty liver disease are the manifestation of the metabolic syndrome at the level of the hepatic parenchyma [*Bedogni G et al., 2007; Kim CH, Zobair M, 2008; Drapkina OM et al., 2010; Tarquini R et al., 2010*].

Remodeling of target organs in hypertensive patients with combined pathology remains poorly investigated.

The objective was to conduct a comparative study of the structural and functional state of heart, vessels and liver in patients with isolated essential hypertension and in terms of its combination with type 2 diabetes or obesity.

Materials and methods

One hundred fifty eight patients, who gave written informed consent to participate in the study and met the inclusion criteria, were examined at the Department of therapy and nephrology of Kharkiv Medical Academy of Postgraduate Education. The study groups were selected based on the criteria presented
in Table 1.

The first group consisted of 35 essential hypertension patients with DM2 and normal body weight, the second consisted of 38 essential hypertension patients with DM2, overweight or I degree obesity. The third group consisted of 30 essential hypertension patients without DM2 with normal body weight. The fourth group consisted of 35 essential hypertension patients without DM2, overweight and I degree obesity. All the groups were matched for age, sex, essential hypertension stage, arterial hypertension grade, and functional class of the chronic heart failure. The control group consisted of 20 healthy individuals, who had no signs of essential hypertension, DM2 and obesity after comprehensive clinical and instrumental examination.

Standard biochemical methods deteined glucose concentration in venous blood, glycosylated hemoglobin (HbA1c), and lipid profile.

Ultrasound examinations were performed on ULTIMA RA cardiac ultrasound scanner (Radmir Company, Ukraine) in one-, two-dimensional and Doppler modes with color mapping by conventional methods. Volumes of the left atrium and right atrium, end-systolic diameter and end-diastolic diameter of the left ventricle, end-diastolicpressure in the left ventricle, left ventricle ejection fraction, index of relative wall thickness, and myocardial mass index of left ventricle were measured.

Left ventricle diastolic function was assessed subsequent to the examination results of blood flow in the pulmonary artery and transmitral diastolic flow in the pulsed and tissue Doppler modes with the definition of the following parameters: maximum rate of early left ventricle filling (E), the maximum speed of late (atrial) left ventricle filling (A), the ratio of the maximum velocity of early and late left ventricle filling (E/A), left ventricular isovolumic relaxation time, deceleration time of early diastolic flow velocity, the average pulmonary artery pressure according to Kitabatake A. [*Kitabatake A et al., 1983*], the ratio of peak **e** and **E** on the mitral valve in spectral and tissue Doppler modes (E/e).

All the patients underwent endothelium-dependent vasodilatation degree assessment in reactive hyperemia in order to examine endothelial function. Examinations were conducted with 5-12 *MHz* broadband linear transducer in Doppler color mapping
three times on the left and right brachial artery in 15-minute intervals between samples, using the method of Celermajer D.S. (1994) modified by Ivanova O.V. (1998). The maximum vasodilation of the brachial artery normally has to exceed 10% of the original diameter. Simultaneously, we

Table 1

The criteria for selection of patients in research

Inclusion criteria	***Exclusion criteria***
· age range of 45-60; · essential hypertension stage II, grade 2 · DM2 moderate, subcompensated · I–II functional class chronic heart failure · body mass index: ✓ normal weight - 18-24.9 *kg/m2* ✓ overweight - 25-29.9 *kg/m2* ✓ I degree obesity - 30-34.9 *kg/m2* ✓ abdominal obesity (IDF criteria, 2005): ✓ waist circumference for men > 94 *cm* for women > 80 *cm*, · normal glomerular filtration rate · normal creatinine levels · absence of proteinuria (only microalbuminuria is admissible) · established duration of: ✓ essential hypertension for 8-12 years, ✓ DM2 for 3-7 years, and	· age below 45 and over 60 · type 1 diabetes mellitus; essential hypertension ✓ obesity for 4-5 years. stage III, grade 3 · III-IV functional class chronic heart failure · DM2 in mild and severe forms in compensation and decompensation phases · insulin therapy in patients with type 2 diabetes · II-III degree obesity · presence of comorbidity in patients with essential hypertension and DM2: ✓ acute coronary syndrome ✓ myocardial infarction ✓ arrhythmias and conduction ✓ rheumatic heart disease

- ✓ systemic connective tissue diseases
- ✓ cancer diseases
- ✓ symptomatic hypertension
- ✓ thyroid disease, acute inflammation
- · reduced glomerular filtration rate, proteinuria
- · unsatisfactory ultrasound scan
- · patients' refusal from participation in the study

measured the intima-media thickness of the carotid artery (2 *cm* proximal to the bifurcation of the common carotid artery). Pulse wave velocity by the carotid artery was determined with W-Track- method (phase tracking method, patented by scanner manufacturers). Examination of pulse wave velocity in the abdominal aorta (on the left subclavian artery to the femoral artery) was performed using a phased transducer with a frequency of 2-4 *MHz*. For the shiftwave elastography of liver we used ULTIMA RA scanner (Radmir Company, Ukraine) with function elastography and convex sensor at 1-5 *MHz*. The magnitude of stiffness of the liver parenchyma (Elast) was expressed in terms of Young's modulus values in kilopascals (E, *kPa*).

Statistical data processing was performed using Statistics for Windows 6.0 software. The tables demonstrate average values and errors of average values.

Results and discussion

The results of the study showed that the groups of patients are characterized by preserved left ventricle
systolic function, as evidenced by the values of ejection fraction of the left ventricle in the normal range. Other indicators of ultrasound except left ventricle end systolic and end diastolic, left ventricle ejection fraction and deceleration time in patients of all the groups differed significantly from the control values ($p<0.05$) [*Abel ED et al., 2008; Kochueva MN et al., 2014*].

The comparative analysis of the studied parameters in groups I and II (essential hypertension patients in combination with DM2 with normal weight and obesity) are shown in Table 2.

The patients with essential hypertension and DM2, whose BMI was just a bit higher (not more than 34.9 *kg/m2*), showed a significant progression in remodeling processes of blood vessels and liver with a significant increase in common carotid artery intima-media thickness, common carotid artery pulse wave velocity, Elast and a significant decrease in amount of endothelium-dependent vasodilatation of the brachial artery ($p<0.05$). The negative dynamic in the values of

Table 2

Structural and functional changes in the target organs of patients with essential hypertension and diabetes mellitus type 2

Index	Group I (n=35)	Group II (n=38)	Control group (n=20)
IMT, *mm* *	0.88±0.01	0.96±0.01**	0.64±0.02
PWV CA, *m/s*	8.15±0.12*	9.12±0.07**	5.83±0.14
PWVAA, *m/s*	8.53±0.12*	9.15±0.09	6.18±0.11
EDVD, %	6.97±0.08*	6.10±0.06**	13.01±0.20
LV EDD, *mm*	4.89±0.04	5.03±0.03	4.51±0.04
LV ESD, *mm*	3.20±0.03	3.32±0.02	2.84± 0.03
EF, %	63.60±0.33	62.62±0.26	66.72± 0.75
IRWT, *U*	0.48±0.01*	0.47±0.003	0.36± 0.01
LV MMI, *g/m2*	141.56±2.47*	139.98±2.75	74.44± 2.34
PAP, *mm Hg*	16.38±0.35*	18.40±0.34	11.47± 0.37
E/A, *U*	0.92± 0.02*	0.92± 0.02	1.15± 0.01
DT, *ms*	0.17± 0.02	0.15± 0.003	0.17± 0.004
IVRT, *ms*	0.13± 0.002*	0.11± 0.002	0.09± 0.002

E / e , *U*	6.08±0.14*	6.39±0.11	5.35±0.10
Elast, *kP a*	10.31±0.07*	12.08±0.04**	3.20±0.05

***Notes**: * – the difference between all groups and control group is reliable; ** – the difference between first and second groups is reliable.*

***Abbreviat ions**: **IMT** - intima media thickness, **PWV** - pulse wave velocity, **CA** – carotid artery, **AA** – abdominal aorta, **EDVD** - endothelium-dependent vasodilatation, **LV** – left ventricle, **EDD** - end-diastolic diameter, **ESD** - end-systolic diameter, **EF** – ejection fraction, **IRWT** - index of relative wall thickness, **MMI** - myocardial mass index of left ventricle, **PAP** – pulmonary artery pressure, **DT** - deceleration time, **IVRT** - index of relative wall thickness*

abdominal aorta pulse wave velocity, left ventricle end diastolic and end systolic diameters, pulmonary artery pressure and E/e was not significant (p>0.05). It was explained by the initial phase of obesity when deterioration in structure-functional state of the heart can be moderate [*Abel ED et al., 2008; Kim CH, Zobair M, 2008; Khurs EM, Poddubnaya AV, 2010; Tarquini R et al., 2010*].

The similar situation could be observed when comparing the performance of structure-functional state of the heart, blood vessels and liver in patients from groups 3 and 4 (essential hypertension without DM2). A slight increase in BMI in patients with essential hypertension led to the deterioration in remodeling processes of the target organs, but the degree of negative changes was less than in patients with comorbidity. Significant differences were observed only in terms of endothelium-dependent vasodilatation and Elast (p<0.05). The endothelial dysfunction and hepatic steatosis were the most sensitive markers of organ damage in the presence of increasing body weight in patients with essential hypertension [*Kim CH, Zobair M, 2008; Drapkina OM et al., 2010; Tarquini R et al., 2010*]. The results of the study are presented in Table 3. The results of index comparison in groups 1 and 3 and groups 2 and 4 demonstrated the contribution of DM2 to remodeling of target organs in patients with essential hypertension with normal and elevated body mass.

The results of the study indicated to a significant negative contribution of DM2 to the development and progression of cardiac remodeling, vascular and liver in hypertensive patients, regardless of body weight of patients – the value of all the main parameters studied reflected significantly more pronounced disorders of structural and functional state of organs in patients with DM2 (Table 3).

Table 3

Structural and functional changes in the target organs of patients being studied

Index	Group I (n=35)	Group II (n=38)	Group III (n=30)	Group IV (n=35)	Group VI (n=20)
IMT, *mm*	0.88 ± 0.01*	0.96 ± 0.01	0.82 ± 0.02*	0.84 ± 0.01**	0.64 ± 0.02
PWV CA, *m/s*	8.15 ± 0.12*	9.12 ± 0.07	7.40 ± 0.11*	7.75 ± 0.12**	5.83 ± 0.14
PWVAA, *m/s*	8.53 ± 0.12*	9.15 ± 0.09	8.03 ± 0.13*	8.17 ± 0.10**	6.18 ± 0.11
EDVD, %	6.97 ± 0.08*	6.10 ± 0.06	9.07 ± 0.17*	8.62 ± 0.15**, ***	13.01 ± 0.20
LV EDD, *mm*	4.89 ± 0.04	5.03 ± 0.03	4.75 ± 0.03*	4.89 ± 0.04**	4.51 ± 0.04
LV ESD, *mm*	3.20 ± 0.03	3.32 ± 0.02	3.08 ± 0.02*	3.18 ± 0.03**	2.84 ± 0.03
EF, %	63.60 ± 0.33	62.62 ± 0.26	64.46 ± 0.32	63.87 ± 0.41**	66.72 ± 0.75
IRWT, *U*	0.48 ± 0.01	0.47 ± 0.003	0.47 ± 0.001	0.46 ± 0.004	0.36 ± 0.01
LV MMI, *g/m2*	141.56 ± 2.47	139.98 ± 2.75	127.54 ± 2.93*	122.39 ± 2.37**	74.44 ± 2.34
PAP, *mm Hg*	16.38 ± 0.35	18.40 ± 0.34	12.81 ± 0.39*	14.09 ± 0.27**	11.47 ± 0.37
E / A, *U*	0.92 ± 0.02	0.92 ± 0.02	0.87 ± 0.02*	0.90 ± 0.02	1.15 ± 0.01
DT, *ms*	0.17 ± 0.02	0.15 ± 0.003*	0.26 ± 0.05	0.15 ± 0.004	0.17 ± 0.004
IVRT, *ms*	0.13 ± 0.002	0.11 ± 0.002	0.11 ± 0.003	0.11 ± 0.003	0.09 ± 0.002
E / e , *U*	6.08 ± 0.14	5.67 ± 0.11*	6.39 ± 0.11	5.87 ± 0.23**	5.35 ± 0.10
Elast, *kP a*	10.31±0.07	12.08±0.04	4.07±0.04*	9.74±0.08**, ***	3.20±0.05

Notes: * – the difference between first and third groups is reliable

** – the difference between second and fourth groups is reliable
*** – the difference between third and fourth groups is reliable
Abbreviations: *See table 2 for abbreviations*

Thus, this study made it possible to establish the negative impact of DM2 and weight gain on the development of structural and functional changes of the heart, blood vessels and liver in essential hypertension patients.

Conclusions

The patients with essential hypertension stage II grade 2 without DM2 and in combination with subcompensated moderate DM2, showing the signs of I-II functional class chronic heart failure, are characterized by preserved left ventricle systolic function and deterioration of cardiac structural and functional state of the heart, blood vessels and liver.

Not depending on BMI the patients with essential hypertension and DM2 in the comparison with hypertensive patients had different values of thickness of the intima-media in the carotid arteries (which were significantly higher), different pulse wave velocities in the great vessels, the size of the cavities and myocardial mass of the left ventricle, the integral index of diastolic filling - E/e (integral ratio of maximum velocities of early diastolic filling according to spectral and tissue Doppler examination), the index of rigidity of the liver parenchyma according to shift-wave elastography and significantly lower value of endothelium-dependent vasodilatation of the brachial artery.

Even a slight increase in BMI (not higher than 34.9 *kg/m2*) was associated with a deterioration of endothelial function and structural and functional properties of the heart, blood vessels, and liver, which is more pronounced in terms of comorbidity.

REFERENCES

1. Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. Physiol Rev. 2008; 88: 389-419.

2. American Diabetes Association: Standards of Medical Care in Diabetes 2011. Diabetes Care. 2011; 34(1): 11-61.

3. Ametov AS. [Obesity is the epidemic of the XXI century] [Published in Russian]. Therapeutic Archives. 2002; 10: 5-7.

4. Bagry HS, Raghavendram S, Carli F. Metabolic syndrome and insulin resistance. *Anesthesiology*. 2008; 108(3): 506-523.

5. Bedogni G, Miglioli L, Masutti F., et al. Incidence and natural course of fatty liver in the general population: the Dionysos study. Hepatology. 2007; 46: 1387-1391.

6. Butrova SA. [Metabolic syndrome: pathogenesis, clinical manifestations, diagnosis, treatment approaches] [Published in Russian]. Russian Journal of Medicine. 2012; 20(3): 56-58.

7. Celermajer DS, Sorensen KE, Bull C., et al. Endothelium-dependent dilation in the systemic arteries of asymptomatic subjects relates to coronary risk factors and their interaction. JAm Coll Cardiol. 1994; 24(6): 1468-1474.

8. Cole T, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ. 2000; 320: 1240-1243.

9. Colwell JA. Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome. JAMA. 2011; 306(2): 215.

10. Dedov II, Melnichenko GA. [Obesity] [Published in Russian]. Moscow, 2004: 456 p.

11. Demidova TY. [Atherosclerosis and diabetes type 2: mechanisms and management] [Published in Russian]. Kardiosomatika. 2011; 2: 22-30.

12. Drapkina OM, Gatsolaeva DS, Ivashkin VT. [Nonalcoholic fatty liver disease as a component of the metabolic syndrome] [Published in Russian]. Russian Medical News. 2010; 2: C. 72-78.

13. Gorbas IM, Barna OM, Sakalosh VY., et al. [Assesment of the prevalence and control of risk factors of cardiovascular diseases in the population and physicians] [Published in Ukrainian]. Medicine of Ukraine. 2010; 1: 4-9.

14. Guize L, Thomas F, Pannier B., et al. All- Cause Mortality Associated With Specific Combinations of the Metabolic Syndrome According to Recent Definitions. Diabetes Care. 2007; 30: 2381-2387.
15. Intengan HD, Schiffrin EL. Vascular remodeling in hypertension: roles of apoptosis, inflammation, and fibrosis. Hypertension. 2001; 38: 581-587.
16. Ivanova OV, Rogoza AN, Balakhonova TV., et al. [Determining the response of the brachial artery to endothelium shear stress as an evaluation method for the state of endothelium-dependent vasodilation using high definition ultrasound in patients with arterial hypertension] [Published in Russian]. Cardiology. 1998; 3: 37-40.
17. Khurs EM, Poddubnaya AV. [Echocardiography in the diagnosis of structural and functional status and cardiac remodeling] [Published in Russian]. Ultrasound and functional diagnostics. 2010; 1: 89-100.
18. Kim CH, Zobair M. Nonalcoholic fatty liver disease: a manifestation of the metabolic syndrome. Clev Clinic J Med. 2008; 75(10): 721-728.
19. Kitabatake A, Inoue M, Asao M., et al. Noninvasive evaluation of pulmonary hypertension by a pulsed Doppler technique. Circulation. 1983; 68(2): 302-309.
20. Kochueva MN, Sukhonos VA, Shalimova AS., et al. [The possibility of correcting of structural and functional state of target organs in patients with hypertension and obesity] [Published in Russian]. British Journal of Education and Science. 2014; 1(5): 308-313.
21. Kochueva MN, Sukhonos VA, Shalimova AS., et al. State of integral remodeling parameters of target organs in patients with essential hypertension and obesity. Georgian Medical News. 2014; 6(231): 26-30.
22. Kovalenko VM, Karnatskyi VM. [Diseases of the circulatory system as medical, social and sociopolitical problem. Analytical and statistical manual] [Published in Ukrainian]. Kyiv, 2014: 279 p.
23. Narkiewicz K. Obesity and hypertension – the issue is more complex than we thought. Nephrol Dial Transplant. 2006; 21: 264-267.
24. Pospelov DL. [Arterial hypertension and cardiovascular risk in the practice of the physician] [Published in Russian]. Ukrainian Medical Journal. 2013; 2(94): 6-7.
25. Rabmouni K, Correia ML, Haynes WG., et al. Obesity – associated Hypertension. New insights into mechanisms. Hypertension. 2005; 45: 9-14.
26. Shalimova AS. Contribution of diabetes type 2 in the development of remodeling of heart and vessels in patients with essential hypertension. The New Armenian Medical Journal. 2014; 8, 2: 33-39.
27. Shilov AM, Avshalumov AS, Markovskyi VB., et al. [Risk factors of cardiovascular complications in patients with overweight, combined with arterial hypertension and their correction] [Published in Russian]. RMJ. 2009; 10(349): 678-683.
28. Syrenko YM. [Arterial hypertension and concomitant diseases] [Published in Ukrainian]. Donetsk, 2010: 384p.
29. Tarquini R, Lazzeri C, Boddi M. Non-alcoholic fatty liver disease: a new challenge for cardiologists. G Ital Cardiol. (Rome). 2010; 11(9): 660-669.
30. Thomas F, Bean K, Pannier B., et al. Cardiovascular Mortality in Overweight Subjects. The Key Role of Associated Risk Factors. Hypertension 2005; 46: 654-663.